Original Contribution

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Does Sex Modify the Effect of Endovascular Treatment for Ischemic Stroke?

A Subgroup Analysis of 7 Randomized Trials

Vicky Chalos, MD; Inger R. de Ridder, MD, PhD; Hester F. Lingsma, PhD; Scott Brown, PhD; Robert J. van Oostenbrugge, MD, PhD; Mayank Goyal, MD, PhD; Bruce C.V. Campbell, PhD; Keith W. Muir, MD; Francis Guillemin, MD, PhD; Serge Bracard, MD; Philip White, MD; Antoni Dávalos, MD; Tudor G. Jovin, MD; Michael D. Hill, MD; Peter J. Mitchell, MD; Andrew M. Demchuk, MD; Jeffrey L. Saver, MD; Wim H. van Zwam, MD, PhD; Diederik W.J. Dippel, MD, PhD; on behalf of the HERMES Collaborators

Background and Purpose—Previous studies have reported less favorable outcome and less effect of endovascular treatment (EVT) after ischemic stroke in women than in men. Our aim was to study the influence of sex on outcome and on the effect of EVT for ischemic stroke in recent randomized trials on EVT.

Methods—We used data from 7 randomized controlled trials on EVT within the HERMES collaboration. The primary outcome was 90-day functional outcome (modified Rankin Scale). We compared baseline characteristics and outcomes between men and women. With ordinal logistic regression, we evaluated the association between EVT and 90-day functional outcome for men and women separately, adjusted for potential confounders. We tested for interaction between sex and EVT.

Results—We included 1762 patients in the analyses, of whom 833 (47%) were women. Women were older (median, 70 versus 66 years; $P<0.001$), were smoking less often (30% versus 44%; $P<0.001$), and had higher collateral grades (grade 3: 46% versus 35%; $P<0.001$) than men. Functional independence (modified Rankin Scale score, 0–2) at 90 days was reached by 318 women (39%) and 364 men (39%). The effect of EVT on the ordinal modified Rankin Scale was similar in women (adjusted common odds ratio [acOR], 2.13; 95% CI, 1.47–3.07) and men (acOR, 2.16; 95% CI, 1.59–2.96), with a P for interaction of 0.926.

Conclusions—Sex does not influence clinical outcome after EVT and does not modify treatment effect of EVT. Therefore, sex should not be a consideration in the selection of patients for EVT. **(*Stroke*. 2019;50:00-00. DOI: 10.1161/STROKEAHA.118.023743.)**

Key Words: randomized controlled trial ■ sex ■ stroke ■ thrombectomy

See related articles, p 2285, 2299, 2420

Previous studies have reported less favorable outcome[1–3] and less effect of endovascular treatment (EVT)[4–8] after ischemic stroke among women compared with men. EVT was proven to be safe and effective in a meta-analysis of 5 randomized controlled trials (RCTs) within the Highly Effective Reperfusion Using Multiple Endovascular Devices (HERMES) collaboration.[7] As with the results of new and upcoming clinical trials more patients seem to benefit from EVT, individualized selection of patients for EVT has become of increased

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From the Department of Neurology (V.C., D.W.J.D.), Department of Public Health (V.C., H.F.L.), and Department of Radiology and Nuclear Medicine (V.C.), Erasmus MC University Medical Center the Netherlands; Department of Neurology (I.R.d.R., R.J.v.O.) and Department of Radiology (W.H.v.Z.), Cardiovascular Research Institute Maastricht, Maastricht University Medical Center, the Netherlands; Altair Biostatistics, St. Louis Park, MN (S.B.); Departments of Clinical Neuroscience and Radiology (M.G., M.D.H., A.M.D.), Hotchkiss Brain Institute, Cummings School of Medicine, University of Calgary, Canada; Department of Medicine and Neurology (B.C.V.C.) and Department of Radiology (P.J.M.), Royal Melbourne Hospital, University of Melbourne, Australia; Institute of Neuroscience and Psychology, University of Glasgow, Queen Elizabeth University Hospital, United Kingdom (K.W.M.); Department of Clinical Epidemiology, Inserm (F.G.) and Department of Diagnostic and Interventional Neuroradiology (S.B.), University of Lorraine and University Hospital of Nancy, France; Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, United Kingdom (P.W.); Department of Neuroscience, Hospital Germans Trias y Pujol, Barcelona, Spain (A.D.); Department of Neurology, Stroke Institute, University of Pittsburgh Medical Center Stroke Institute, Presbyterian University Hospital, PA (T.G.J.); and Department of Neurology and Comprehensive Stroke Center, David Geffen School of Medicine, University of Los Angeles, CA (J.L.S.).

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Correspondence to Vicky Chalos, MD, Department of Neurology, Erasmus MC University Medical Center, PO Box 2040, 3000 CA Rotterdam, the Netherlands. Email v.chalos@erasmusmc.nl

importance. This is best done by combining prognostic information from multiple clinical and radiological characteristics.[9] However, uncertainty remains about the size of the treatment effect in specific subgroups, such as in women. In MR CLEAN (A Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands), a significant interaction between sex and EVT was found.[4] Men experienced a major benefit from EVT, whereas no significant treatment effect of EVT was found in women. The meta-analysis of HERMES did not confirm these findings but did not further elaborate on this topic, and baseline characteristics by sex were not reported.[7] Since then, 2 more RCTs on EVT have been added to the HERMES collaboration data.[10,11] We aimed to provide more insight on the influence of sex on outcome and on the effect of EVT for ischemic stroke in patient-pooled data of the 7 RCTs within the HERMES collaboration.

Methods

Study Population and Design

We pooled the data from 1764 participants in the 7 RCTs on EVT within the HERMES collaboration (MR CLEAN,[12] ESCAPE [Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times],[5] EXTEND-IA [Extending the Time for Thrombolysis in Emergency Neurological Deficits - Intra-Arterial],[13] SWIFT PRIME [Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment],[6] REVASCAT [Randomized Trial of Revascularization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke due to Anterior Circulation Large Vessel Occlusion Presenting Within 8 Hours of Symptom Onset],[14] THRACE [Mechanical Thrombectomy After Intravenous Alteplase Versus Alteplase Alone After Stroke],[10] and PISTE [Pragmatic Ischaemic Stroke Thrombectomy Evaluation][11]). These RCTs compared EVT (intervention), primarily performed with stent retrievers, with standard care (control) in patients with an ischemic stroke caused by a large vessel occlusion in the anterior circulation. All participants provided informed consent according to each trial protocol, and each RCT was approved by the local ethics committee. The HERMES protocol and main outcomes have been reported previously.[7,15] HERMES data are available via the VISTA-Endovascular repository.

Outcome Measures

The primary outcome was functional outcome, measured with the modified Rankin Scale (mRS) score, at 90 days. Secondary outcomes were excellent 90-day functional outcome (mRS, 0–1), 90-day functional independence (mRS, 0–2), extent of neurological deficits measured with the National Institutes of Health Stroke Scale (NIHSS) at 24 hours after randomization, successful reperfusion after EVT (modified Thrombolysis in Cerebral Infarction Score ≥2B), and follow-up infarct volume (FIV) on noncontrast CT or magnetic resonance imaging at 12 hours to 2 weeks. Safety outcomes were 90-day mortality and symptomatic intracranial hemorrhage, defined according to each trial protocol.[15]

Statistical Analyses

Patients with missing data on sex were excluded from the analyses. We compared baseline characteristics and outcomes between men and women using descriptive statistics. With generalized linear mixed models, with trial as a random effect, we evaluated the association between EVT and primary and secondary outcomes. FIV was log transformed (log+1) because of its skewed distribution, to best satisfy the linear model. We tested for interaction between sex and treatment allocation using multiplicative interaction terms in the regression model. Regression analyses were adjusted for age, baseline NIHSS, time from onset to randomization, diabetes mellitus, prior stroke, occlusion location, intravenous tPA (tissue-type plasminogen activator) administration, and collateral grade. Missing data in these covariates were imputed with simple imputation, with the exception of collateral grade (≥10% missing data), which was imputed with single imputation with regression based on relevant covariates, trial, and mRS. Unadjusted and adjusted common odds ratios and adjusted betas are reported with 95% CIs, and all *P* are 2-sided. Statistical analyses were performed with SAS software, version 9.4, and R, version 3.3.

Results

After excluding 2 patients with unknown sex, we included 1762 patients in the analyses, of whom 929 (53%) were men and 833 (47%) were women. Women were older (median, 70 versus 66 years; *P*<0.001), were smoking less often (30% versus 44%; *P*<0.001), and had higher collateral grade (grade 3: 46% versus 35%; *P*<0.001) than men (Table 1). There were no differences in medical history, especially atrial fibrillation, prestroke mRS, administration of tPA, and onset to randomization or groin puncture times between women and men.

The median 90-day mRS was the same for women and men in the intervention groups, and for women and men in the control groups, with significant differences between the intervention groups versus the control groups (4.0 versus 3.0; *P*<0.001; Table 2). Functional independence (mRS, 0–2) at 90 days was reached by 318 women (39%) and 364 men (39%), with a similar distribution among the intervention and control groups, significantly in favor of the intervention group (Figure 1; Table 2). Mortality at 90 days was 15% for women and 16% for men. Mortality also did not differ between the intervention and control group for both sexes. There was no difference between women and men in symptomatic intracranial hemorrhage (3.7% versus 3.6%) or in successful reperfusion (75% versus 76%). FIV was smaller in women (32 mL) than in men (53 mL; Table 2). FIV was also significantly smaller in the intervention group than in the control group in both women (27 versus 40 mL; *P*=0.009) and men (39 versus 70 mL; *P*<0.001; Table 2), with an adjusted beta of −0.26 (95% CI, −0.49 to −0.02) and −0.33 (95% CI, −0.50 to −0.15; Table I in the online-only Data Supplement), respectively.

Treatment effect of EVT on the ordinal mRS was comparable in women (adjusted common odds ratio, 2.13; 95% CI, 1.47–3.07) and men (adjusted common odds ratio, 2.16; 95% CI, 1.59–2.96) with a *P* for interaction of 0.926 (Figure 2). Similarly, there was no difference between women and men in the effect of any of the additional secondary outcomes (Figure 2; Table I in the online-only Data Supplement).

Discussion

In this individual patient data meta-analysis that included 1762 patients with ischemic stroke from multiple centers in multiple countries, treatment effects of EVT on functional outcome and other clinical, imaging, and safety outcome measures were similar in women and men.

To date, one study (MR CLEAN), which was also included in the current analysis, has previously addressed the same research question.[4] Contrary to the results of the present analysis, a significant interaction between sex and treatment effect in favor of men was found. Although in MR CLEAN, women had more unfavorable baseline characteristics, more serious adverse

Table 1. Baseline Characteristics by Sex*

Characteristics	Women (n=833)	Men (n=929)	*P* Value
Age, y	70 (58–77), 833	66 (57–74), 928	<0.001
Systolic blood pressure, mm Hg	145±26, 829	145±23, 924	0.945
Hypertension	58% (479/830)	55% (509/926)	0.248
Hyperlipidemia	36% (289/812)	40% (362/906)	0.065
Diabetes mellitus	16% (130/830)	17% (157/925)	0.477
Atrial fibrillation	34% (218/641)	32% (229/709)	0.524
Prior stroke	9.9% (82/829)	12% (106/921)	0.280
Smoking	30% (230/765)	44% (367/842)	<0.001
Blood glucose, mg/dL	136±97, 596	130±43 (665)	0.142
NIHSS	17 (13–20), 826	17 (14–21), 925	0.027
Prestroke mRS			0.141
0	81% (486/603)	84% (571/677)	
1	14% (82/603)	12% (80/677)	
≥2	5.8% (35/603)	3.8% (26/677)	
ASPECTS	8.0 (7.0–9.0), 820	8.0 (7.0–9.0), 916	0.077
Intravenous tPA administration	89% (740/833)	90% (832/929)	0.645
Interhospital transfer	21% (177/830)	25% (234/926)	0.051
Occlusion location†			0.336
ICA	26% (200/765)	27% (242/883)	
M1	65% (497/765)	65% (576/883)	
M2	8.6% (66/765)	7.4% (65/883)	
Collateral grade†			<0.001
0—absent collateral vessels	0.2% (1/599)	1.9% (13/691)	
1—<50% filling of occluded area	13% (75/599)	18% (124/691)	
2—>50% but <100% filling of occluded area	42% (249/599)	45% (309/691)	
3—100% filling of occluded area	46% (274/599)	35% (245/691)	
Onset to randomization, min	182 (138–242), 831	184 (142–247), 924	0.289
Onset to tPA administration, min	120 (89–161), 736	115 (80–158), 828	0.117
Onset to groin puncture, min	240 (184–300), 369	238 (185–295), 415	0.670

ASPECTS indicates Alberta Stroke Program Early CT Score; ICA, internal carotid artery; IQR, interquartile range; M1, middle cerebral artery segment 1; M2, middle cerebral artery segment 2; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and tPA, tissue-type plasminogen activator.

*Categorical variables are presented in percentage (n/N) and continuous variables in mean±SD, n, or median (IQR), n.

†Occlusion location and collateral grade: central reading.

events, and higher mortality than men, a play of chance was suggested because these differences seemed to be insufficient to explain the lack of an overall treatment effect in women. A study on sex-based group differences in RCTs showed that statistically significant sex-treatment interactions are only slightly more frequent than what would be expected by chance.[16] This underpins the idea that the significant sex-treatment interaction observed in MR CLEAN was indeed a play of chance. Our results, which indicate that sex does not modify treatment effect of EVT in ischemic stroke, support previous findings of ESCAPE, EXTEND-IA, and HERMES, which all performed a subgroup analysis by sex but did not report baseline characteristics and secondary analyses by sex, that there are no differences in treatment effect of EVT on functional outcome between women and men.[5–7] Our results are also in line with an analysis in patients with acute basilar artery occlusion, where no significant sex differences for outcome and recanalization were observed, regardless of treatment with tPA (with or without EVT) or EVT alone.[8] Also, several post hoc analyses based on pooled data from RCTs have shown that sex does not modify the treatment effect of tPA on clinical outcome.[17–20]

Clinical and safety outcomes also did not differ between women and men in the intervention group, which is similar to the findings of several previous studies that have assessed sex

Table 2. Outcome Measures for All Patients (Intervention+Control) by Sex, and by Sex and Treatment Allocation*

Outcome Measures	Intervention+Control			Women			Men		
	Women (N=833)	Men (N=929)	*P* Value	Intervention (N=412)	Control (N=421)	*P* Value	Intervention (N=459)	Control (N=470)	*P* Value
Clinical outcomes									
mRS at 90 d	3.0 (2.0–4.0), 820	3.0 (2.0–4.0), 922	0.724	3.0 (1.0–4.0), 408	4.0 (2.0–5.0), 412	<0.001	3.0 (1.0–4.0), 458	4.0 (2.0–5.0), 464	<0.001
mRS 0–1 at 90 d	23% (190/820)	23% (210/922)	0.864	30% (121/408)	17% (69/412)	<0.001	29% (133/458)	17% (77/464)	<0.001
mRS 0–2 at 90 d	39% (318/820)	39% (364/922)	0.768	48% (195/408)	30% (123/412)	<0.001	48% (219/458)	31% (145/464)	<0.001
NIHSS at 24 h	11 (4.0–18), 796	12 (5.0–18), 892	0.098	8.0 (3.0–16), 393	14 (7.0–19), 403	<0.001	9.0 (4.0–17), 442	14 (8.0–19), 450	<0.001
Imaging outcomes									
mTICI post-EVT†‡			0.383						
0	7.2% (25/346)	9.1% (35/383)							
1	2.0% (7/346)	3.1% (12/383)							
2A	16% (55/346)	12% (45/383)							
2B	67% (231/346)	67% (256/383)							
3	8.1% (28/346)	9.1% (35/383)							
FIV at 12 h to 2 wk, mL†	32 (12–99.5)	53 (15–141)	<0.001	27 (11–91), 388	40 (16–106), 393	0.009	39 (12–120), 433	70 (21–155), 451	<0.001
Safety outcomes									
Mortality at 90 d	15% (128/827)	16% (152/925)	0.602	16% (64/411)	15% (64/416)	1.000	14% (64/459)	19% (88/466)	0.051
sICH	3.7% (30/817)	3.6% (33/910)	1.000	4.5% (18/404)	2.9% (12/413)	0.268	3.1% (14/448)	4.1% (19/462)	0.480

EVT indicates endovascular treatment; FIV, follow-up infarct volume; IQR, interquartile range; mRS, modified Rankin Scale; mTICI, modified Thrombolysis in Cerebral Infarction; NIHSS, National Institutes of Health Stroke Scale; and sICH, symptomatic intracranial hemorrhage.

*Categorical variables are presented in percentage (n/N) and continuous variables in median (IQR), n.

†mTICI post-EVT and FIV: central reading.

‡mTICI post-EVT only available for the intervention group.

differences in functional outcome after EVT,[21–23] with the exception of one study, which found that in patients treated with EVT, women were less likely to be independent at 90 days.[24]

Other studies, from before the implementation of EVT, have reported poorer stroke-related outcomes in women than in men, independently of treatment.[1,3,25] However, in the

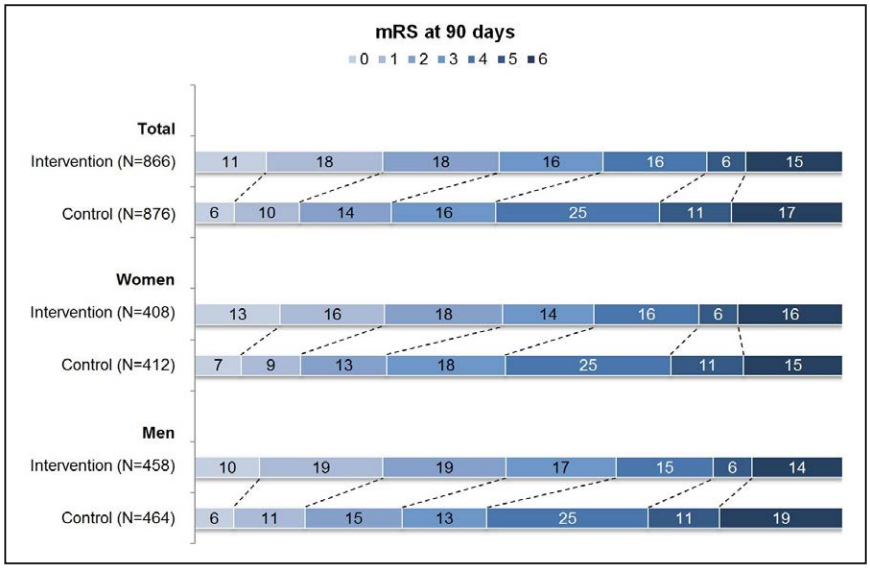

Figure 1. Distribution of the modified Rankin Scale (mRS) score in percentages among the intervention and control group, for all patients and by sex. mRS was missing in 5 patients of the intervention group (4 women and 1 man) and in 15 patients of the control group (9 women and 6 men).

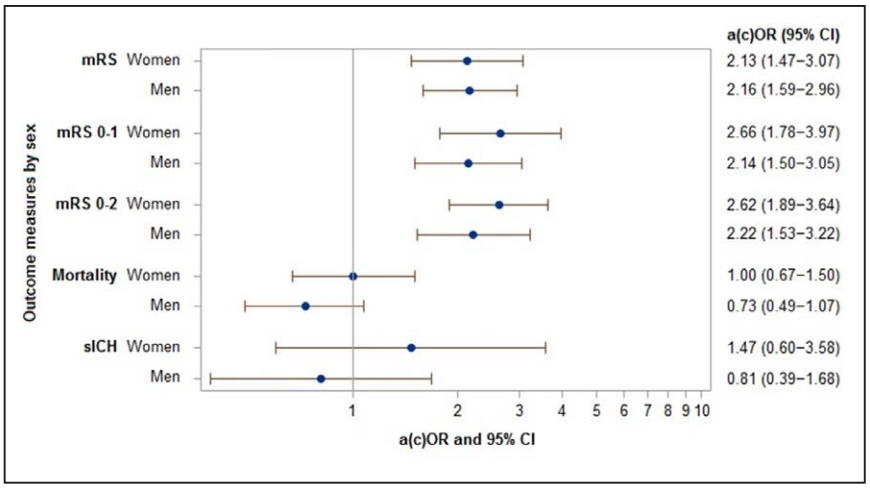

Figure 2. Forest plot showing adjusted treatment effect (adjusted [common] odds ratios [a(c)ORs] and 95% CI) of endovascular treatment (EVT) per outcome measure for women and men. Adjusted for age, baseline NIHSS, time from onset to randomization, diabetes mellitus, prior stroke, occlusion location, intravenous tPA administration, collateral grade, and trial (as random effect). mRS indicates modified Rankin Scale; and sICH, symptomatic intracranial hemorrhage.

present study, 90-day functional independence and mortality were equal among women and men, also for those in the control groups only. An explanation for the difference between previous literature and our study may be selection, visible in the somewhat different baseline characteristics of women in our study compared with previous reports. In our study, for example, occurrence of atrial fibrillation was equal between women and men, while the prevalence of ischemic stroke caused by atrial fibrillation is usually higher in women.[26] Moreover, the NIHSS score at baseline was lower in women than in men and collateral grade was higher.

To the best of our knowledge, no research has been done on a possible association of sex with collateral grade, and not many studies have previously described baseline collateral grade by sex in patients eligible for EVT. The higher baseline collateral grade in women, which might be the result of selection, is in line with the findings of an analysis done in MR CLEAN.[27] In IMS III (Interventional Management of Stroke III Trial), which evaluated EVT+tPA versus tPA alone, no difference in collateral grade was found between women and men.[28] As a higher collateral grade is associated with smaller FIVs after EVT,[29–31] the smaller FIVs in women in our study might be correlated with the higher baseline collateral grade in women as well. However, this did not impact 90-day functional outcome in women. We think that the difference in FIV and in baseline collateral grade between men and women might not have been large enough explain a possible better outcome in women. Moreover, outcome is not dependent on FIV or baseline collateral grade alone but on multiple variables (together), including age, prestroke disability, time, recanalization status, and notably the NIHSS score at 24 hours, which is a strong predictor of outcome and did not differ between women and men.

Women are often underrepresented in (stroke) clinical trials. In the present study, women, eligible for EVT, were also less often included than men (47% versus 53%), even though more women than men experience a stroke in high-income countries,[25] and large vessel occlusions (in the anterior circulation) seem to occur more often in women than in men.[32,33] This may be the result of selection because clinical trials tend to select younger patients with lower baseline NIHSS scores. In a nonclinical trial setting, in 2 studies performed after the HERMES main results, 52% and 56% of all patients treated with EVT were women.[23,24] Moreover, women seem to be less likely to receive any acute reperfusion therapy for (ischemic) stroke.[34–36] This may be caused by various factors identified as being more common in women with ischemic stroke than in men, such as older age, higher prestroke disability, living alone, and higher occurrence of aphasia and reduced level of consciousness at presentation, which are also risk factors for late arrival.[1,2,37,38] These factors could reduce the use of and access to acute reperfusion therapy in women. Future studies should focus on whether there are clinically relevant sex differences in the incidence of large vessel occlusion and use of and access to EVT, which was also emphasized in a review on sex differences in ischemic stroke.[39]

A limitation of this study is the use of RCT data instead of data from more recent registries and surveys representing the current clinical practice. However, the use of RCT data made it possible to analyze potential differences in treatment effect of EVT between women and men and resolve the uncertainty that still existed about the treatment benefit of EVT in women. This would have been difficult, if not at all possible, if we had used observational data. Moreover, by using RCT data, we were able to control for numerous factors that were measured in a consistent, rigorous manner. Another limitation is lack of information about marital status. Marital status is known to be related to baseline sex differences, such as longer onset to randomization times (reflecting prehospital delays) in women, and could impact outcome.

We conclude that sex does not influence clinical outcome after EVT for ischemic stroke and that women and men benefit equally from EVT. Sex should, therefore, not be a consideration in the selection of patients for EVT.

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in the study and had final responsibility for the decision to submit for publication.

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